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Prognostic value of routinely available data in patients with stable coronary heart disease. A 10-year follow-up of patients sampled at random times during their disease course

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ABSTRACT

Objective To characterise the long-term prognosis of patients with stable coronary artery heart disease by means of 'standard predictors' defined as demographic, clinical and biochemical quantities routinely available in general practices and ascertained at an interview not prompted by renewed cardiac complaints.

Methods This is an observational study based on data from 2199 Copenhagen placebo patients from the 'clarithromycin for patients with stable coronary heart disease' trial of patients with stable coronary heart disease. In the trial, we compared the effects of 14 days of clarithromycin treatment versus placebo. The predictors were based on the interview forms and blood samples collected at entry, along with demographic information from hospital files.

We studied 'standard predictors' of a composite outcome (myocardial infarction, unstable angina, cerebrovascular disease or all-cause death) and of all-cause death. Using Cox regression, we compared predictions of status at 3, 6 and 9 years without and with the use of 'standard predictors' and used receiver operating characteristic statistic.

Results Few 'standard predictors' were associated ($p<0.01$) with the composite outcome or with all-cause death. When no 'standard predictors' were included, 63.2% of the model-based predictions of the composite outcome and 79.9% of death predictions were correct. Including all 'standard predictors' in the model increased the figures to 68.4% and 83.4%, respectively. *C* indices were low, except when all-cause death was assessed as a single outcome where *C* was 0.79.

Conclusion 'Standard predictors' routinely available in general practices contribute only modestly to risk assessment in consecutively sampled patients with stable coronary heart disease as ascertained at a contact not prompted by renewed cardiac complaints. Novel biomarkers may improve the assessment.

Trial registration number NCT00121550.

Key questions

What is already known about this subject?

- Patients with stable coronary artery disease are at an increased risk of death or non-fatal cardiovascular incidents.

What does this study add?

- New knowledge regarding the long-term impact of routinely measured, demographic, clinical and biochemical factors for the prediction of non-fatal cardiovascular incidents and all-cause death in patients with stable coronary heart disease ascertained at baseline review not prompted by renewed cardiac complaints.
- Routinely measured, demographic, clinical and biochemical factors do show an expected association with long-term course, but the prognostic impact is weak. For useable prognostic differentiation, stronger clinical markers are needed.

How might this impact on clinical practice?

- High-risk patients with stable coronary heart disease presenting in a general practice with non-cardiac complaints may be identified using 'standard predictors' and advanced biomarkers and referred to further examinations by specialist cardiologists.

INTRODUCTION

It would be of great practical value if the long-term prognosis of patients with stable coronary heart disease could be assessed by the general practitioner at a random time during the patient's disease course, that is, when the visit at the general practitioner is not prompted by acute symptoms or made during recovery from a major cardiovascular event. To be practically useful, the assessment should be based on information routinely available to the general practitioner. The term 'stable coronary heart disease' calls for a definition that is readily applied in general practice. In the 'clarithromycin for patients with stable coronary heart disease' (CLARICOR)

trial,[1 2] we have developed the operational definition described below, covering a common and important class of patients.

Our present objective, therefore, is to use the data from the CLARICOR trial to identify relevant prognostic quantities, readily available during clinical routine work, when a patient with stable coronary heart disease is seen by the practising physician for *reasons other than renewed cardiac complaints*. Such quantities may prove useful as a background for closer investigation of selected patients. The present analysis also serves as a background for a search for additional prognostic covariates which may be available in the biobank of the CLARICOR trial. A detailed account of methodology and statistical analysis was published before the analysis commenced.[3]

MATERIALS

Patients

In the CLARICOR trial, 13 702 patients aged 18–85 years who had a discharge diagnosis of myocardial infarction or angina pectoris during 1993–1999 and were alive in August 1999 were invited by letter for a 14-day trial of clarithromycin versus placebo.[1 2] Of the 13 702 patients, 6116 accepted the invitation. Of these, 177 refused to participate and 1567 were excluded while 4372 were randomised.

Baseline data were obtained from the hospital files and patient interviews at six cardiology clinics covering the Copenhagen area. Initial follow-up lasted for 2.6 years, during which outcomes were collected through hospital and death registries and assessed by an adjudication committee.[2] Corresponding register data later showed to produce similar results.[4 5] The adjudicated outcomes were therefore replaced and augmented by register outcomes to cover 10 years of follow-up. Biochemical data were obtained from analysis of serum from the CLARICOR biobank collected at randomisation and stored at −80°C.

The patients excluded from the trial were those who fulfilled the following conditions: (1) suffered from acute myocardial infarction or unstable angina pectoris within the previous 3 months; (2) had percutaneous transluminal coronary angioplasty and coronary bypass surgery within the previous 6 months; (3) with impaired renal, or (4) hepatic dysfunction, (5) congestive heart failure (New York Heart Association (NYHA) IV classification of heart failure), or (6) active malignancy; (7) without capacity to manage own affairs; and (8) without breast feeding or possible pregnancy.

The main results of the CLARICOR trial were that clarithromycin increased the risk of cardiovascular as well as all-cause death.[1 6–8] Therefore, we here focus on the placebo group.

Predictors

Data material collected from the 2199 placebo patients was covering the period until 31 December 2009, that is, 10 years (±3 months), and was obtained by use of public registers with almost 100% coverage,[4 5] as explained in the Outcomes section and in refs 4–6.

Demographic and anamnestic data

Enrolment interviews provided smoking status, current medication and known hypertension or diabetes, while information concerning sex, age and history of myocardial infarction or unstable angina pectoris was obtained from the local hospital files.

Biochemical measurements on plasma collected at entry

Biochemical measurements on plasma collected at entry included lipoproteins,[9] high-sensitivity C-reactive protein (hs-CRP/mg/L)[10] and glomerular filtration rate (GFR/mL/min) using creatinine.[11] Along with variables already mentioned, these quantities are those collectively referred to as 'standard predictors' and specified in table 1.

Outcomes

We assessed the time from randomisation until the first occurrence of one of the following events: acute myocardial infarction, unstable angina pectoris, cerebrovascular disease and all-cause death (the composite outcome) and the time from randomisation to all-cause death. The algorithm used to get from the International Statistical Classification of Diseases used in the national registries[12 13] to the events of the composite outcome is described in refs 4 5.

METHODS

Statistical analysis

We used the Cox proportional hazards model supplemented by Breslow estimation of the baseline hazard and using SAS V.9.4 in agreement with our peer-reviewed, published statistical analysis plan.[3] The model assumptions were tested using Bonferroni adjusted p values.[3 14]

There are virtually no missing data from entry information in the CLARICOR trial[3] but 9.4% of the patients had one or more laboratory test values missing. We used Little's test to decide whether to use multiple imputation or a complete case analysis.[15]

All analyses that included covariates were stratified by centre. For each covariate, we examined if it interacted significantly with sex (using a Bonferroni adjustment).

Inference analyses

If an HR showed a deviation from 1.00 such that p<0.01, we classified the variable as a prognostic predictor, given the outcome analysed and the other covariates included in the analysis. We identified the prognostic predictors among the 'standard predictors' for each of the two outcomes, the predictor being tested when used alone in a Cox regression analysis (except for age, see below) and when used in combination with the remaining 'standard predictors'.[3]

Assessing the prognostic utility of the 'standard predictors'

We used the Cox-Breslow method to estimate the survival curve of the outcome of each patient using all available

Table 1 The distributions of standard predictors in the placebo group and in the group of patients who received clarithromycin

Standard predictors	Placebo patients (n=2199)	Clarithromycin patients (n=2172)
Demographics and history		
Sex (male), n (%)	1518 (69.0)	1514 (69.7)
Age/year, mean (SD)	65.2 (10.4)	65.4 (10.3)
Smoking status (smoking, ex-smoker, never smoked), n (%)	Smokers, 753 (34.2) Ex-smokers, 1011 (46.0) Never smoked, 435 (34.2)	Smokers, 819 (37.6) Ex-smokers, 982 (45.2) Never smoked, 371 (17.1)
Hypertension, n (%)	883 (40.2)	878 (40.4)
Diabetes, n (%)	337 (15.3)	341 (15.7)
Previous AMI, n (%)	1494 (67.9)	1470 (67.7)
Current medication		
Aspirin, n (%)	1937 (88.1)	1902 (87.6)
Beta-blocker, n (%)	681 (31.0)	653 (30.1)
Calcium antagonist, n (%)	772 (35.1)	755 (34.8)
ACE inhibitor, n (%)	577 (26.3)	604 (27.8)
Long-lasting nitrate, n (%)	457 (20.8)	453 (20.9)
Diuretics, n (%)	773 (35.2)	762 (35.1)
Digoxin, n (%)	126 (5.7)	154 (7.1)
Statins, n (%)	904 (41.1)	896 (41.3)
Antiarrhythmic drugs, n (%)	51 (2.3)	55 (2.5)
Biochemical predictors		
Log (CRP/mg/L) mean (SD), n*	1.03 (1.12) 2159	1.07 (1.15) 2128
ApoA1/mg/dL mean (SD), n	1.70 (0.34) 2076	1.70 (0.36) 2041
Log (ApoB/mg/dL) mean (SD), n	0.16 (0.27) 2075	0.15 (0.27) 2040
Chol-HDL/mmol/L mean (SD), n	1.02 (0.32) 2074	1.02 (0.32) 2039
Chol-LDL/mmol/L mean (SD), n	2.56 (0.72) 2079	2.55 (0.73) 2044
Log(cholesterol/mmol/L) mean (SD), n	1.73 (0.20) 2075	1.72 (0.20) 2039
Log(triglyceride/mmol/L) mean (SD), n	0.73 (0.53) 2078	0.71 (0.52) 2040
Glomerular filtration rate (GFR/mL/min) mean (SD), n	71.8 (19.2) 2079	72.1 (19.2) 2044

*The value of n varies because the laboratory tests have missing values.
AMI, acute myocardial infarction; Chol, cholesterol; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Log, natural logarithm.

information. From the curve, we read off the probabilities that the patient will be event free at time T=3, 6 and 9 years. If the probability is larger than or equal to 0.5, we make the favourable (F) prediction that the patient is still event free at time T; otherwise, we make the unfavourable (un-F) prediction that the patient experiences an event before T. The truth values of the predictions were determined by comparison with the observed records. To assess the role of the covariates in these predictions we repeated the procedure without introducing any covariates (the Cox output then reduces to a Kaplan-Meier curve). Here we used methods that do not allow time-dependent covariates, so in this case stratification on age was used (cutting at 60 and 75 years) and age was excluded as a covariate.[16]

We also analysed data using a parametric, accelerated failure time model. For the underlying time-to-event distribution type of the accelerated failure time model, we considered several choices using *q-q* graphs to assess the fit[14] (p 100). The generalised gamma model gave a perfect fit for the composite outcome and a reasonable fit for all-cause mortality.

Using the events observed during the first 9 years of follow-up, the prognostic differentiation was characterised by receiver operating characteristics (ROC) and 'predictive impact' diagrams.[17–19] The hazard estimation is based on the full 10-year follow-up of 1998 patients with complete covariate data but the ROC analysis is limited to what happened to them within the 9-year window.

The calculations involve a prognostic rule being applied to the same data sample from which it was derived. But model fit is assessable (see the ROC diagram).

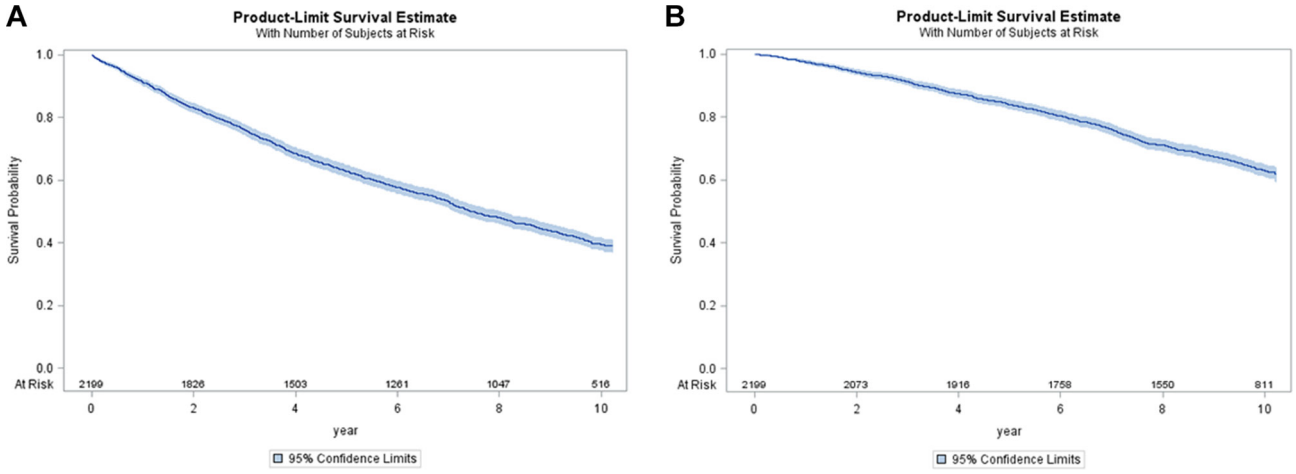

Figure 1 (A) Kaplan-Meier estimate (with 95% CI) of composite outcome including acute myocardial infarction, unstable angina pectoris, cerebrovascular disease, and all-cause death. Figures below the curve are biannual number at risk in the placebo group of the CLARICOR trial. (B) Kaplan-Meier estimate (with 95% CI) of the outcome all-cause death. Figures below the curve are biannual number at risk in the placebo group of the CLARICOR trial.

RESULTS

As Little's test[15] had p=0.93, we used complete case analyses in the following.

Table 1 presents an overview of the covariates expected to be available from patients with stable cardiovascular disease during clinical routine work ('standard predictors'). We have shown the corresponding data of the clarithromycin group to illustrate that the randomisation was successful. It appears that the results are consistent across the placebo group and the clarithromycin group. Figure 1 presents the Kaplan-Meier curves for the composite outcome (figure 1A) and all-cause death (figure 1B). At 2 years, 1826 (83.0%) had not yet suffered a composite outcome and 2073 (94.3%) were still alive. At 6 years, 1261 (57.3%) had not yet suffered a composite outcome and 1758 (79.9%) were still alive. At 9 years, the numbers are 969 (44.9%) and 1487 (67.6%), respectively. In the following we shall describe the differentiation of these risks offered by the covariates presented in table 1.

Testing the 'standard predictors'

As the proportional hazards assumption was violated for age we included an interaction between age at entry and time (since randomisation) in the inference analyses.

Table 2 shows the HR of each of the 'standard predictors' when used alone in a Cox analysis (table 2, columns 2–4) and when used in combination with the rest of the 'standard predictors' for the composite outcome (table 2, columns 5–7). The main effect of age is only significant when no adjustment by the 'standard predictors' is used. By contrast, the interaction between age and time is significant with and without adjustment. Smoking habits, diabetes, most of the medication indicators, log (hs-CRP) and reduced GFR predict the risk of the composite outcome when used alone (the threshold of p<0.01). In the analysis that included all the 'standard predictors', smoking habits, diabetes, long-lasting nitrate medication, digoxin medication and GFR provided prognostic information.

Table 3, whose structure is the same as that of table 2, shows the results for all-cause death. When each predictor is assessed alone, the results are much like those for the composite outcome. Smoking habits, diabetes, most of the medication indicators, log (hs-CRP) and reduced GFR predict the risk of all-cause death when used alone (p<0.01). When all 'standard predictors' are included, male sex now becomes also significantly unfavourable in association with smoking habits, diuretic medication, digoxin medication, log (hs-CRP) and reduced glomerular filtration rate. The biochemical lipid quantities were not prognostic.

For neither outcome did any standard predictor interact significantly with sex.

Prognostic impact of the 'standard predictors'

Table 4 (columns 2–3) shows the types, numbers and percentages of correct predictions obtained when we used the Cox model and the composite outcome without covariates included (column 2) and when the 'standard predictors' (and age strata, see the Methods section) were included. The percentages are correct predictions over total number of predictions made (three per patient unless dropout, see footnote §, table 4). Without covariates included in the model, 63.2% of the predictions were correct. With 'standard predictors' included, 68.4% became correct, increasing the number of correct predictions by only 5.2%, and leaving 31.6% in error.

For the all-cause death outcome (see table 4, lower half, left side), the corresponding percentages were 79.9%, 83.4%, 3.5% and 16.6%, respectively. So, it appears that the contributions of the individual's own routine data (the 'standard predictors') to the predictions are rather modest.

Table 2 Composite outcome including acute myocardial infarction, unstable angina pectoris, cerebrovascular disease and all-cause death. HRs of standard predictors when used alone and when used in combination with the rest of the standard predictors

	Single predictor examined in the model (stratified by centre)			All standard predictors in the model (stratified by centre)		
Standard predictors	**HR**	**95% CI of HR**	**P values**	**HR**	**95% CI of HR**	**P values**
Demographics and history						
Sex (male=1)	1.004	0.889 to 1.134	0.95	1.150	1.005 to 1.315	0.042
Age/year	1.024	1.013 to 1.034	<0.0001	1.013	1.001 to 1.025	0.030
Age·time*/year·year	1.00374	1.002 to 1.006	0.0004	1.004	1.002 to 1.006	<0.0001
Smoking status (ex-smoker compared with never smoking)	1.203	1.026 to 1.410	0.0062	1.210	1.025 to 1.428	<0.0001
Smoking status (smoking compared with never smoking)	1.309	1.110 to 1.545		1.547	1.300 to 1.842	
Hypertension, Y/N	1.105	0.985 to 1.239	0.090	0.991	0.870 to 1.129	0.89
Diabetes, Y/N	1.318	1.133 to 1.533	0.0003	1.261	1.076 to 1.480	0.0043
Previous AMI, Y/N	1.169	1.033 to 1.324	0.014	1.151	1.012 to 1.308	0.032
Current medication						
Aspirin, Y/N	0.978	0.820 to 1.165	0.80	1.021	0.852 to 1.225	0.82
Beta-blocker, Y/N	1.010	0.893 to 1.141	0.88	1.013	0.888 to 1.155	0.85
Calcium antagonist, Y/N	1.232	1.095 to 1.385	0.0005	1.121	0.982 to 1.279	0.090
ACE inhibitor, Y/N	1.246	1.099 to 1.412	0.0006	1.054	0.916 to 1.213	0.46
Long-lasting nitrate, Y/N	1.738	1.527 to 1.978	<0.0001	1.348	1.172 to 1.551	<0.0001
Diuretics, Y/N	1.613	1.437 to 1.810	<0.0001	1.180	1.030 to 1.352	0.017
Digoxin, Y/N	2.212	1.805 to 2.711	<0.0001	1.576	1.269 to 1.957	<0.0001
Statins, Y/N	0.746	0.663 to 0.839	<0.0001	0.883	0.769 to 1.014	0.077
Antiarrhythmic drugs, Y/N	1.119	0.763 to 1.642	0.56	0.924	0.627 to 1.362	0.69
Biochemical predictors						
Log(CRP/mg/L)	1.171	1.113 to 1.232	<0.0001	1.070	1.014 to 1.480	0.014
ApoA1/mg/dL	0.905	0.764 to 1.072	0.25	0.707	0.516 to 0.969	0.031
Log(ApoB/mg/dL)	1.165	0.938 to 1.447	0.17	0.826	0.413 to 1.651	0.59
Chol-HDL/mmol/L	0.954	0.794 to 1.147	0.62	1.104	0.714 to 1.708	0.66
Chol-LDL/mmol/L	1.027	0.948 to 1.112	0.52	0.912	0.751 to1.107	0.35
Log (cholesterol/mmol/L)	1.247	0.940 to 1.654	0.13	1.786	0.577 to 5.525	0.31
Log (triglycerides/mmol/L)	1.024	0.919 to 1.141	0.67	1.030	0.878 to 1.208	0.72
Glomerular filtration rate (GFR/mL/min)	0.985	0.982 to 0.988	<0.0001	0.995	0.991 to 0.999	0.0084

*Time is years since randomisation.
AMI, acute myocardial infarction; Chol, cholesterol; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, hypertension is not present; Y, hypertension is present.

Table 4 (columns 4 and 5) shows the corresponding results obtained when we used the accelerated failure time model. These results are very similar to those obtained using the Cox model.

Table 5 shows the *C* indices for the composite outcome and its components, describing concordance as to whether patients were to experience the event in question (within the 9-year window). The underlying ROC curve is given in figure 2Afor all-cause death. The empirical curve (dashed) shows that the 644 deaths and 1354 survivals closely fit the predicted pattern (smooth curve).

Figure 2Bholds a 'predictive impact' graph, designed to compare the predictive power of rival prognostic rules. The diagram estimates the benefit that might accrue by treating high-risk patients if a completely effective preventive intervention existed. The patients are ordered according to assigned risk (just as in the ROC). As a function of the percentage imagined to be selected for treatment (abscissa), the ordinate shows how many deaths (dashed) and life-years (fat curve) would be saved. Within the 9-year window, the 644 deaths will cause 2703 years to be lost without treatment. From the graph it may be read

Table 3 All-cause death. HRs of standard predictors when used alone and when used in combination with the rest of the standard predictors

	Single predictor examined in the model (stratified by centre)			All 'standard predictors' in the model (stratified by centre)		
Standard predictors	**HR**	**95% CI of HR**	**P values**	**HR**	**95% CI of HR**	**P values**
Demographics and history						
Sex (male=1)	0.970	0.831 to 1.132	0.70	1.329	1.119 to 1.578	0.0012
Age/year	1.065	1.046 to 1.084	<0.0001	1.047	1.027 to 1.068	<0.0001
Age·time*/year·year	1.00305	1.000056 to 1.0061	0.045	1.004	1.001 to 1.007	0.011
Smoking status (ex-smoker compared with never smoking)	1.366	1.109 to 1.683	0.0071	1.436	1.155 to 1.786	<0.0001
Smoking status (smoking compared with never smoking)	1.379	1.109 to 1.714		2.135	1.692 to 2.693	
Hypertension, Y/N	1.117	0.965 to 1.293	0.14	1.001	0.848 to 1.181	0.99
Diabetes, Y/N	1.456	1.211 to 1.751	<0.0001	1.410	1.161 to 1.713	0.0005
Previous AMI, Y/N	1.166	0.995 to 1.368	0.058	1.161	0.985 to 1.369	0.075
Current medication						
Aspirin, Y/N	0.854	0.689 to 1.059	0.15	0.898	0.718 to 1.124	0.35
Beta-blocker, Y/N	0.926	0.790 to 1.084	0.34	0.916	0.773 to 1.085	0.31
Calcium antagonist, Y/N	1.193	1.028 to 1.385	0.020	0.999	0.845 to 1.181	0.99
ACE inhibitor, Y/N	1.349	1.153 to 1.579	0.0002	1.056	0.886 to 1.258	0.54
Long-lasting nitrate, Y/N	1.776	1.513 to 2.084	<0.0001	1.178	0.991 to 1.400	0.063
Diuretics, Y/N	2.183	1.889 to 2.524	<0.0001	1.432	1.210 to 1.694	<0.0001
Digoxin, Y/N	3.008	2.388 to 3.790	<0.0001	1.826	1.428 to 2.334	<0.0001
Statins, Y/N	0.597	0.511 to 0.697	<0.0001	0.812	0.675 to 0.976	0.027
Antiarrhytmic drugs, Y/N	1.113	0.677 to 1.830	0.67	0.798	0.482 to 1.320	0.38
Biochemical predictors						
Log(CRP/mg/L)	1.283	1.202 to 1.370	<0.0001	1.147	1.070 to 1.230	0.0001
ApoA1/mg/dL	1.089	0.878 to 1.351	0.44	0.928	0.615 to 1.401	0.72
Log(ApoB/mg/dL)	0.923	0.704 to 1.210	0.56	0.483	0.202 to 1.156	0.10
Chol-HDL/mmol/L	1.192	0.947 to 1.501	0.13	0.884	0.503 to 1.551	0.67
Chol-LDL/mmol/L	0.958	0.865 to 1.060	0.41	0.982	0.772 to 1.250	0.88
Log (cholesterol/mmol/L)	1.169	0.819 to 1.668	0.39	1.895	0.455 to 7.899	0.38
Log (triglycerides/mmol/L)	0.868	0.755 to 0.997	0.045	0.882	0.716 to 1.086	0.24
Glomerular filtration rate (GFR/mL/min)	0.972	0.969 to 0.976	<0.0001	0.990	0.985 to 0.994	<0.0001

*Time is years since randomisation.
AMI, acute myocardial infarction; Chol, cholesterol; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, hypertension is not present; Y, hypertension is present.

that if 10% of the patients were to be treated with a 100% effective intervention, 29% of the total loss of years may be saved.

DISCUSSION

In this study, we assessed the predictive value of 'standard predictors' routinely available for a general practitioner when he/she meets a patient with stable coronary heart disease whose visit is not prompted by renewed cardiac complaints. When no 'standard predictors' were included in the prediction, 63.2% of the model-based predictions of the composite outcome and 79.9% of all-cause death predictions were correct. Including all 'standard predictors' in the model increased the figures to 68.4% and 83.4%, respectively.

We have not been able to identify a study where death of all causes and cardiovascular insults have been assessed in patients with (1) stable coronary heart disease of a type like the above described, (2) with a 10-year follow-up, and (3) where the clinical examination was not prompted by renewed cardiovascular complaints. Taken together, most of the studies we identified were either analysing

Table 4 The types and numbers of correct predictions obtained when the Cox proportional hazards model was used and when the accelerated failure model (using generalised gamma distribution) was used. For comparison, the results without covariates included are shown

	Statistical model used			
	Cox proportional hazards model†		Accelerated failure model (using generalised gamma distribution)	
Type of predictions*	No covariates	Covariates included	No covariates	Covariates included
	Composite outcome‡			
True favourable predictions, n (%) (out of a total of 5970 predictions made)§	2658 (44.5)	2910 (48.7)	2658 (44.5)	2918 (48.9)
True unfavourable predictions, n (%) (out of a total of 5970 predictions made)	1115 (18.7)	1174 (19.7)	1115 (18.7)	1197 (20.0)
Total number of true predictions, n (%) (out of a total of 5970 predictions made)	3773 (63.2)§	4084 (68.4)	3773 (63.2)	4115 (68.9)
	All-cause death			
True favourable predictios, n(%) (out of a total of 5970 predictions made)	4768 (79.9)	4585 (76.8)	4768 (79.9)	4563 (76.4)
True unfavourable predictions, n (%) (out of a total of 5970 predictions made)	0 (0)¶	392 (6.57)	0 (0)	401 (6.72)
Total number of true predictions, n (%) (out of a total of 5970 predictions made)	4768 (79.9)	4977 (83.4)	4768 (79.9)	4964 (83.1)

*For each patient at time (T) equal to 3, 6 and 9 years and using the patient's individual survival curve the predicted outcome (patient 'alive at T' (favourable outcome) compared with patient 'not alive at T' (unfavourable outcome)) was read off the survival curve and the results compared with the observed outcome. When no covariates were included in the model, the Kaplan-Meier survival curve was used to calculate the predictions.
†Time-dependent covariates were not allowed in the SAS V.9.4 program used. To allow for the fact that age violated the proportional hazard assumption we stratified by age categories (see text) in addition to centre and excluded age from the covariates.[21]
‡Comprising acute myocardial infarction, unstable angina pectoris, cerebrovascular disease and all-cause death.
§n is the number of true predictions made. The per cent is n over the total number of predictions made. 5970 predictions are made, namely 1998 patients with complete covariates times three time points (at 3, 6 and 9 years) minus 24 predictions not checkable due to patients lost to registries. Of these predictions, a total of 3773 were true which amounts to 3773/5970=63.2%.
¶As total mortality is <50%, all predictions are automatically favourable (and 79.9% of them pertain to a so far survivor).

small study samples, for example,[20] were developed in patients with acute coronary syndromes,[21] or had short follow-up.[22]

In many respects, our patients are like those of the Prospective Observational Longitudinal Registry of Patients with Stable Coronary Heart Disease (CLARIFY) study[23] which enrolled 20 291 patients of whom 20% had anginal symptoms corresponding to the 20% of our patients who took long-lasting nitrates. Patients with hospital admission for cardiovascular reasons (including revascularization) in the past 3 months before enrolment or conditions interfering with life expectancy such as cancer and NYHA class 4 were excluded. So, in these respects, the CLARIFY patients are like our patients. However, the CLARIFY patients had been observed with a median of 24.1 months and enrolment took place 10 years later than in the CLARICOR trial. A total of 469 cardiovascular deaths or myocardial infarctions occurred in these patients (2.3%).[23] By contrast, in our cohort the corresponding numbers found during the first 2 years of observation were 170 cardiovascular deaths and 7.7%, respectively, probably reflecting improved quality of treatment and more frequent statin treatment in the CLARIFY patients (84% vs only 41% in the CLARICOR patients).

Many of our 'standard predictors' showed that they contained statistically significant prognostic information. However, few of the 'standard predictors' contributed statistically significant prognostic information when all predictors were tested simultaneously. Moreover, the 'standard predictors' offered little prognostic discrimination.

Methodology

Regarding our methodology, the performance statistics reported here are minimal, but they suffice to show that the results are meagre, leaving room for improvement with advanced biomarkers.[3] Prediction at 3, 6 and 9 years covers the follow-up as well as would a sophisticated integral over continuous time. Using 0.50 as a probability threshold is again a least arbitrary choice (the relative impact of false and true predictions being unknown), as is the ROC principle. Adding realism to the naked construct of a 'completely effective preventive intervention' (figure 2B) would again be subject to criticism in the absence of alternatives, with solid empirical backing.

Table 5 Receiver operating characteristic (ROC) areas (*C* indices) of placebo patients with complete records (n=1998). Nine-year risks assigned by the Cox analysis using all standard predictors

Outcome	Ordinary ROC area (event Yes compared with No, regardless of time)	Dynamic C index*
Acute myocardial infarction (AMI)	0.643	0.651
Unstable angina pectoris (UAP)	0.637	0.616
Cerebrovascular disease (CVD)	0.606	0.680
Cardiovascular death (non-cardiovascular death)	0.761 (0.736)	0.730 (0.728)
All-cause death	0.792	0.737
Composite outcome†	0.711	0.640

*When a patient had no event of the kind concerned within the 9-year window, we define: toe (time of event) = + ∞. Then, *C* is the frequency of concordant risks (equal risk weighs 1/2) among patient pairs whose toe data allow us to decide who died first: *C*=freq {concordant risks (or equal risk, 0.5) | sign of toe difference known from data}.
†Consists of acute myocardial infarction, unstable angina pectoris, cerebrovascular disease and all-cause death.

Strengths

The strengths of the CLARICOR trial are the considerable size of the patient population, the long duration of follow-up, few losses to follow-up (0.5%), the ethnic homogeneity of the patient population, rarity of missing values, with focus on an operationally defined, homogeneous and relevant patient category. The design implies that the patients are sampled at random, presumably uneventful, time points during their stable state (as defined by the CLARICOR trial). Furthermore, the large biobank formed during the trial allows an extensive search for new advanced biomarkers to be made.

Limitations

Among those 7586 patients who declined our invitation to visit a cardiology centre, many must have been eligible for the CLARICOR trial, and we do not know how they looked and fared. With a response rate of about 50%, the cohort could represent a prognostic elite if responders were mostly mobile and health-conscious patients. So, selection bias cannot be excluded.

Furthermore, the patients recruited for the CLARICOR trial were diagnosed with coronary heart disease about 20 years ago. Because of the tremendous developments in treatment and rehabilitation, there has been a very significant and graded increase in prognosis of such patients,[24] as shown in national data.[25] Given these uncertainties, prognostic findings in the CLARICOR cohort should not directly be applied to present-day patient materials. However, the overall picture regarding the relative predictive effect of 'standard predictors' and advanced biomarkers should provide relevant and valuable information.

Potential weaknesses of the present cohort within the context of prognostication of patients with stable coronary heart disease as here defined include the lack of information about left ventricle function, body mass index and blood pressure, as well as the effects of changes in medications during follow-up. Information about postinfarction heart failure and postinfarction angina pectoris was not available to us. But information about the medication at entry into CLARICOR served as proxy information. The lack of left ventricular ejection fraction may be partially or completely compensated, as Solomon *et al*[26] found that age, sex, hypertension, prior acute myocardial infarction, creatinine, diuretics and digoxin were related to left ventricular ejection fraction, all quantities that we have included within the group referred to as 'standard

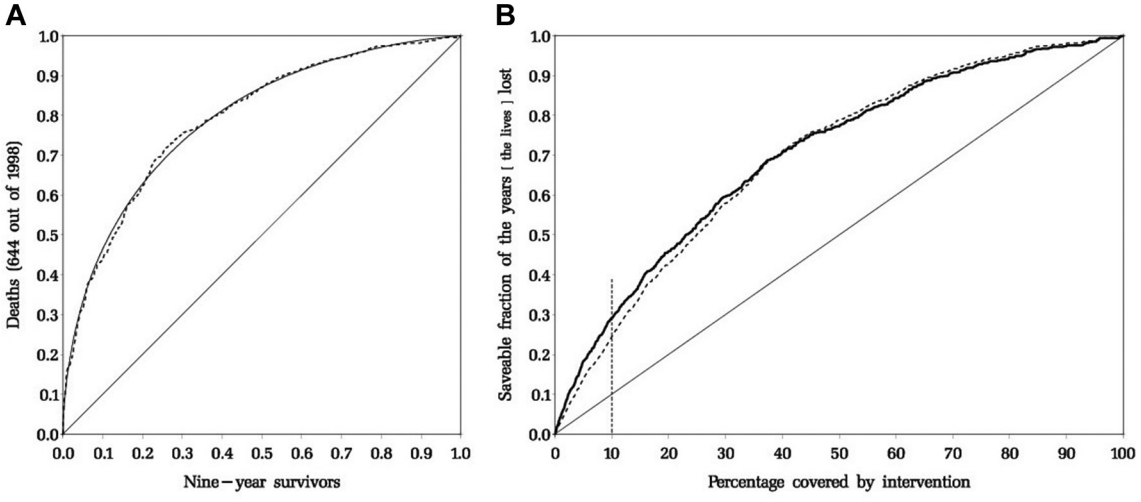

Figure 2 (A) ROC diagram (death vs survival at 9 year data). (B) Predicted imapct curves. ROC, receiver operating characteristic.

predictors'. The shortcomings of our data files are mitigated by the fact that by design the present study focuses on the situation where patients with stable coronary heart disease visit a physician for reasons unrelated to the coronary heart disease. Here it might be of value if simple clinical information readily available could be used to screen these patients with stable coronary heart disease to identify high-risk patients who might be referred to a more thorough cardiologic examination and follow-up.

It was our hope that the simple 'standard predictors' of table 1 might serve this purpose, but they proved too little informative. Behind this disappointing feature lie undoubtedly a meshwork of behavioural and statistical interconnections that are impossible to unravel. A reviewer has pointed out that 'index event' phenomena[27–29] may also be involved. Briefly, to develop an index event (say, infarction), those with a given low-risk trait tend to have unrecorded high-risk traits, and vice versa, so, to the extent that risk traits are permanent, high-low follow-up comparisons will be biased when based on such patients. While this is true, there is no prognostic bias here as the index event is part of the definition of the population of interest.

Furthermore, patients, if any, who became eligible for the CLARICOR trial during the period 1993–1999 and then died before August 1999, are absent. Thus, our data do not represent patients as they *enter* a stable disease state (as delimited by CLARICOR exclusion criteria); instead, they may be regarded as community patients (subject to some self-selection) seen by their physician on a random date during their stable state.

Our model was tested using the same data that were used to derive it. Therefore, we do not feel it is advisable to use the results for predictive purposes without using some independent data to calibrate the model, and for this and the above-mentioned reasons we have elected not to present an explicit prediction model.

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